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An Efficient and Regioselective Synthesis of Tetrazoles under Transition - Metal Free Conditions

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Abstract

A novel protocol for synthesisof series of tetrazoles is demonstrated via in-situformed secondary amides under transition-metal free conditions. The reaction well tolerates a wide variety of functional groups to afford structurally diverse tetrazoles in good to excellent yields at 70°C. All the synthesized compounds were characterized by FT- IR, ^{1}H /^{13}C NMR, LC-Mass spectral data and elemental analyses.

Keywords: *Diamine; Piperonal; Tetrazole.*

1. INTRODUCTION

Tetrazole and its derivatives were found to possess several biological activities including antiallergic (Ikeda *et al.* 1992; Imai *et al.* 2016), antimicrobial activity (Varadharaji *et al.* 2010; Dai *et al.* 2015; Feinn *et al.* 2017), antihypertensive activity, antiinflammatory activity (Mohite *et al.* 2010),central nervous system stimulant activity (Shin-ichi *et al.* 1997), antitubercular activity (Ademac *et al.*2005) etc. The numerous biological activities of tetrazoles are considered due to their distinctive characteristic properties, *viz.*, (i) a close similarity is observed between the acidity of the tetrazole group and the carboxylic acid group (Meanwell, 2011; Allen *et al.* 2012; Pagacz-Kostrzewa *et al.* 2012) and (ii) the tetrazole function is metabolically stable than that acid function. This aspect has been considered a primary driving force for the continual research in the area of tetrazole chemistry.

2. RESULTS & DISCUSSIONS

To test our hypothesis, we treated piperonal, hydrazine hydrate with benzoyl chloride in the presence of PCl_5 and NaN_3 as model substrates under metal free condition. Pleasingly, the reaction was successful and afforded the desired tetrazoles. Nevertheless, the yield of expected tetrazole is very low. Hence, the reaction conditions were optimized to achieve the yield and find out the most suitable conditions for the synthesis of aryl tetrazole. We investigate the various reaction parameters such as solvents, base and temperature to achieve suitable conditions and the results are summarized in Table 1-Table 3.

Table 1. Effect of solvents

Entry	Solvent	Yield (%)
1	Ethanol	75
2	Methanol	68
3	n-Propanol	62
4	Toluene	63
5	DMF	55
6	DMAc	57
7	DMSO	56

Table 2. Effect of bases

Entry	Base	Yield (%)
1	No base	12
2	KOH	75
3	K_2CO_3	66
4	NaOH	70
5	Na_2CO_3	63
6	Pyridine	52
7	Piperidine	29
8	Triethylamine	41

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The screening of a series of solvents indicated that polar solvents such as DMSO and DMF disfavored the desired transformation and that ethanol was the best reaction media (Table 1). Subsequently, the increasing volume of solvent did not affect the yield of tetrazole. Next, variety of organic and inorganic bases were utilized this reaction. The selected reaction was also proceeded in the absence of base, in such case we obtained lower quantity of the product. Incorporating various inorganic bases such as KOH, NaOH, K_2CO_3, Na_2CO_3, were effectively increases the titledproduct and found KOH is the best one. However, organic bases such as pyridine, piperidine and triethylamine were did not increase the yield of target product (table 2). The expected product was not obtained when the reaction was carried out in the absence of PCl_5. Thus prove the vital role of PCl_5 in the conversion of *in-situ* formed secondary amide to tetrazole.

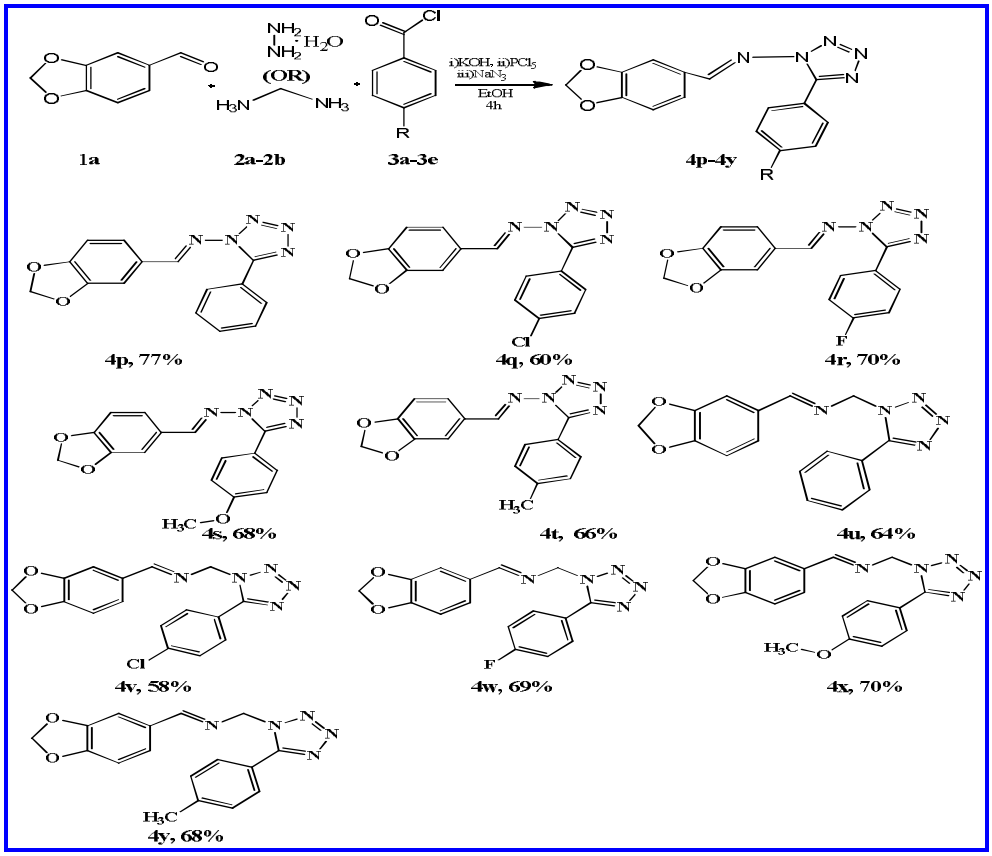
The effect of temperature on the synthesis of tetrazole was undertaken. Initially, the chosen reaction was performed at room-temperature, where in no reaction was occurred and hence the same reaction was studied by increasing the temperature from 50-90 °C. Higher yield was obtained at 70 °C. A dramatic decrease in yield was observed when the reaction temperature was raised from 90 °C to 110 °C. Therefore, 70 °C was chosen for this reaction.

Table 3. Effect of temperature

Entry	Temperature(°C)	Yield (%)
1	RT	No reaction
2	40	50
3	50	59
4	60	61
5	70	77
6	80	73
7	90	68

With this optimized reaction conditions in hand we then examined the scope of aroylchlorides and diamine. A variety of diamine and aroylchlorides possessing either electron-donating or –withdrawing groups. The optimized reaction conditions were found to be applicable to a broad range of substrates (Table 4).

Table 4. Synthesis of tetrazole derivatives



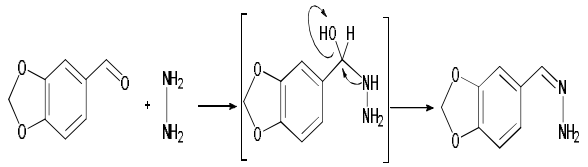
Generally, all the diamines **(2a-2b)** and aroylchlorides **(3a-3e)** underwent above resulting protocol smoothly and afforded expected tetrazoles in good yields. In all the cases, the reactions proceeded in an excellent regioselective manner and provided only a particular regioisomer as single product. At the outset**,** hydrazine hydrate**(2a)**was allowed to react with piperonal and substituted benzoyl chlorides **(3a-3e)** underwent this reaction successfully and provided **4p-4t** in 77-60% of isolated yields. Among those, unsubstituted benzoyl chloride gave 77% of tetrazole.

After that, the reaction of **1a** with methylene diamine **(2b)** and aroyl chlorides **(3a - 3e)** gave **4u -4y** in an excellent yield (58 -70%). 70% of the tiled product was obtained by using 4-methoxybenzoyl chloride. The present exploration has virtues over the existing protocols in metal catalysts were employed. Simplistic manner of synthesis, use of simple and commercially available reagents, ease of isolation of products and milder reaction conditions are the unique features of this method.

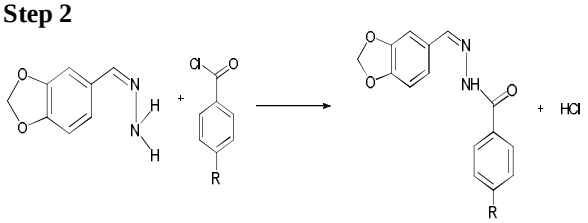
3. REACTION MECHANISM

The proposed reaction mechanism involves three steps. The first step involved the condensation reaction of piperanol with diamine to form Schiff base. Initially, the amine nitrogen acts as a nucleophile, attacking the carbonyl carbon. This is closely analogous to hemiacetal and hemiketal formation. In the next step, Schotten-Baumann reaction of Schiff base derived from step 1 with benzoyl chloride provided secondary amide. In the final step, secondary amide initially reacts with PCl_5 and gives an intermediate. This intermediate further reacted with NaN_3 to yield expected tetrazole through cyclization process.

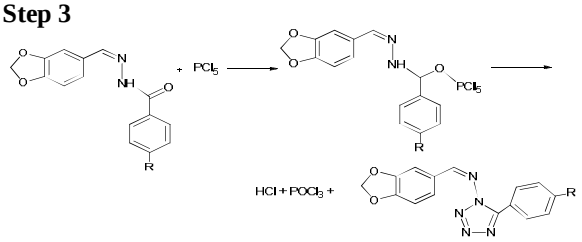
Step 1



Step 2



Step 3



4. EXPERIMENTAL

4.1 General information

All the reagents were purchased from Sigma-Aldrich. Solvents were purchased from Finar chemicals and purified prior to use. The reactions were monitored by analytical TLC on silica gel G/GF 254 plates, and column chromatography was performed with 60-120 mesh silica gel. Melting points were determined on a veego (India) capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer FT-IR spectrometer by using KBr. ^1H and ^{13}C NMR spectra were recorded in Bruker 300 and 75 MHz spectrometer.

4.2 General procedure for the synthesis of compounds 4p-4y

To a stirred solution of benzo[1,3]dioxole-5-carbaldehyde **1a** (0.005 mol), diamines **2a-2b** (0.005 mol) and benzoyl chlorides **3a-3e** (0.005 mol) were added and refluxed for 4 h at 70 °C. To this reaction mixture KOH (1 mmol), PCl_5 (0.001 mol) and NaN_3 (0.005 mol) were added and stirred for 6 h at 80 °C. The reaction progress was monitored by TLC by using ethyl acetate-hexane (80:20%). After the completion of the reaction, the solvent was evaporated in vacuo and the residue was diluted with CH_2Cl_2 (50 mL) and washed with saturated NH_4Cl (20 mL) and water (20 mL).Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using n-hexane/ethyl acetate as eluent.

(E)-N-(benzo[d][1,3]dioxol-5-ylmethylene)-5-phenyl-1H-tetrazol-1-amine (4p)

Anal. Calcd. (%) for$C_{15}H_{11}N_5O_2$: C, 61.43 ; H, 3.78 ; N, 23.88. Found (%):C, 61.41 ; H, 3.75 ; N, 23.86; Yellow Solid; m.p. 89-91°C; R_f = 0.53; FT-IR (KBr, cm^{-1}): 1603, 1571; ^1H NMR (300 MHz, $CDCl_3$, δ/ppm): 8.52 (s, 1H), 7.60-6.58 (m, 8H) 6.04 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6, δ/ppm): 164.26, 160.22, 147.47, 129.72, 129.59, 127.81, 124.63, 115.20, 115.12, 114.91, 108.09, 105.49, 101.22; LC-MS (m/z): 293. 3567.

(E)-N-(benzo[d][1,3]dioxol-5-ylmethylene)-5-(4-chlorophenyl)-1H-tetrazol-1-amine(4q)

Anal. Calcd. (%) for $C_{15}H_{10}ClN_5O_2$: C, 54.97 ; H, 3.08 ; N, 21.37. Found (%):C, 54.95 ; H, 3.06 ; N, 21.35; Yellow solid;m. p. 96-97°C; R_f= 0.48; ; FT-IR (KBr, cm^{-1}): 1601, 1585; ^{1}H NMR (300 MHz, $CDCl_3$, δ/ppm): 8.53 (s, 1H), 7.44-7.11 (m, 7H) 7.17 (d, *J* = 8.0 Hz, 2H), 6.83 (d, *J* = 8.0 Hz, 2H), 6.02 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6, δ/ppm): 163.96, 160.24, 147.49, 146.04, 129.74, 129.61, 127.83, 124.65, 115.22, 114.93, 108.11, 105.51, 101.24; LC-MS (m/z): 327.6845.

(E)-N-(benzo[d][1,3]dioxol-5-ylmethylene)-5-(4-fluorophenyl)-1H-tetrazol-1-amine (4r)

Anal. Calcd. (%) for $C_{15}H_{10}FN_5O_2$: C, 57.88 ; H, 3.24 ; N, 22.50; Found (%):C, 57.87 ; H, 3.22 ; N, 22.49; Yellow solid; m. p. 92-93°C; R_f = 0.54; FT-IR (KBr, cm^{-1}): 1603, 1582; ^{1}H NMR (300 MHz, $CDCl_3$, δ/ppm): 8.54 (s, 1H), 7.45-6.85 (m, 7H), 6.02 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6, δ/ppm): 164.30, 160.26, 149.58, 147.51, 129.76, 129.63, 128.71, 127.85,124.67, 115.24, 115.16, 114.95, 108.13, 105.53, 101.26; LC-MS (m/z): 311.3412.

(E)-N-(benzo[d][1,3]dioxol-5-ylmethylene)-5-(4-methoxyphenyl)-1H-tetrazol-1-amine (4s)

Anal. Calcd. (%) for $C_{16}H_{13}N_5O_3$: C, 59.44 ; H, 4.05 ; N, 21.66; Found (%):C, 59.42 ; H, 4.03 ; N, 21.64; Yellow solid; m. p. 98-99°C; R_f = 0.42; FT-IR (KBr, cm^{-1}): 1602, 1574; ^{1}H NMR (300 MHz, $CDCl_3$, δ/ppm): 8.53 (s, 1H), 7.44-7.25 (m, 5H), 6.86 (d, *J* = 8.0 Hz, 2H), 6.02 (s, 2H), 3.81 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6, δ/ppm): 164.10, 159.28, 147.14, 128.78, 128.65, 126.87, 123.69, 114.26, 113.97, 107.15, 104.55, 100.28, 53.88; LC-MS (m/z): 323.1851.

(E)-N-(benzo[d][1,3]dioxol-5-ylmethylene)-5-(p-tolyl)-1H-tetrazol-1-amine (4t)

Anal. Calcd. (%) for $C_{16}H_{13}N_5O_2$: C, 62.53 ; H, 4.26 ; N, 22.79; Found (%):C, 62.51 ; H, 4.25 ; N, 22.77; Yellow solid;m. p. 87-88°C; R_f = 0.57; FT-IR (KBr, cm^{-1}): 1602, 1575 ; ^{1}H NMR (300 MHz, $CDCl_3$, δ/ppm): 8.53 (s, 1H), 7.38-7.10 (m, 5H), 6.82 (d, *J* = 8.0 Hz, 2H), 6.05 (s, 2H), 2.40 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6, δ/ppm): 163.90, 160.18, 148.04, 129.68, 129.55, 127.77, 124.59, 115.16, 114.87, 108.05, 105.45, 101.18, 21.85; LC-MS (m/z): 307.9128.

(E)-N-(benzo[d][1,3]dioxol-5-ylmethylene)-1-(5-phenyl-1H-tetrazol-1-yl)methanamine (4u)

Anal. Calcd. (%) for $C_{16}H_{13}N_5O_2$: C, 62.53; H, 4.26; N, 22.79; Found (%):C, 62.51 ; H, 4.25 ; N, 22.80; White solid; m. p.112-114°C; R_f = 0.38; FT-IR (KBr, cm^{-1}): 1604, 1587 ; ^{1}H NMR (300 MHz, $CDCl_3$, δ/ppm): 8.14 (s, 1H), 7.52-6.78 (m, 8H), 5.98 (s, 2H), 3.89 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6, δ/ppm): δ161.66, 149.73, 148.15, 130.97, 124.29, 107.96, 106.50, 101.35, 61.39; LC-MS (m/z): 307.5497.

(E)-N-(benzo[d][1,3]dioxol-5-ylmethylene)-1-(5-(4-chlorophenyl)-1H-tetrazol-1-yl) methanamine (4v)

Anal. Calcd. (%) for $C_{16}H_{12}ClN_5O_2$: C, 56.23; H, 3.54; N, 20.49; Found (%):C, 56.22 ; H, 3.51 ; N, 20.50; White solid; m. p.119-121°C; R_f = 0.53; FT-IR (KBr, cm^{-1}): 1623, 1571;^{1}H NMR (300 MHz, $CDCl_3$, δ/ppm): 8.23 (s, 1H), 7.60-6.87 (m, 7H), 5.99 (s, 2H), 3.92 (s, 2H);^{13}C NMR (75 MHz, DMSO-d_6, δ/ppm): 161.75, 149.82, 148.24, 131.06, 128.59, 126.91, 124.38, 122.04, 108.05, 106.59, 101.44, 61.48; LC-MS (m/z): 341.1987.

(E)-N-(benzo[d][1,3]dioxol-5-ylmethylene)-1-(5-(4-fluorophenyl)-1H-tetrazol-1-yl) methanamine (4w)

Anal. Calcd. (%) for$C_{16}H_{12}FN_5O_2$: C, 59.08; H, 3.72; N, 21.53; Found: C, 59.11 ; H, 3.69 ; N, 21.50; White solid; m. p. 124-125°C; R_f = 0.58; FT-IR (KBr, cm^{-1}): 1610, 1582 ; ^{1}H NMR (300 MHz, $CDCl_3$, δ/ppm): 8.13 (s, 1H), 7.79-6.83 (m, 7H), 5.97 (s, 2H), 3.88 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6, δ/ppm): 161.86, 154.09, 152.58, 149.93, 148.35, 131.17, 130.54, 129.95, 124.49, 122.15, 108.16, 106.70, 101.55, 61.59; LC-MS (m/z): 325. 6385

(E)-N-(benzo[d][1,3]dioxol-5-ylmethylene)-1-(5-(4-methoxyphenyl)-1H-tetrazol-1-yl)methanamine (4x)

Anal. Calcd. (%) for $C_{17}H_{15}N_5O_3$: C, 60.53; H, 4.48; N, 20.76; Found: C, 60.52 ; H, 4.46 ; N, 20.75; White solid;m. p.129-130°C; R_f = 0.56; FT-IR (KBr, cm^{-1}): 1608, 1589; ^{1}H NMR (300 MHz, $CDCl_3$, δ/ppm): 8.11 (s, 1H), 7.41-6.29 (m, 7H), 5.99 (s, 2H), 3.88 (s, 3H), 3.87 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6, δ/ppm): 161.87, 153.90, 149.74, 148.16, 130.98, 130.35, 129.76, 124.30, 121.96, 107.97, 106.51, 101.36, 61.40, 55.14; LC-MS (m/z): 337.0789

(E)-N-(benzo[d][1,3]dioxol-5-ylmethylene)-1-(5-(p-tolyl)-1H-tetrazol-1-yl)methanamine (4y)

Anal. Calcd. (%) for $C_{17}H_{15}N_5O_2$: C, 63.54; H, 4.71; N, 21.79; Found (%):C, 63.51 ; H, 4.70 ; N, 21.78; White solid;m. p. 132-133°C; R_f = 0.59; FT-IR (KBr, cm^{-1}): 1611, 1598; ^{1}H NMR (300 MHz, $CDCl_3$, δ/ppm): 8.10 (s, 1H), 7.84-6.55 (m, 7H), 5.98 (s, 2H), 3.88 (s, 2H), 2.48 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6, δ/ppm): 161.69, 153.89, 149.73, 148.18, 130.98, 130.36, 129.75, 124.30, 121.95, 107.93, 106.50, 101.35, 76.58, 61.39, 20.44; LC-MS (m/z): 321.1036.

5. CONCLUSION

In summary, we have demonstrated a metal-free protocol for the synthesis of tetrazole derivatives from the reactions of piperonal, diamine and aroyl chlorides in a one-pot fashion. FT- IR, ^{1}H/ ^{13}C NMR and LC-MS studies were utilized for the structural conformation of all the synthesized products. The present strategy features high chemo- and regioselectivity and excellent tolerance for a wide range of functional groups. Moreover, the combinational use of PCl_5 and NaN_3 has been demonstrated to be robust to activate the C=O bond of secondary amide and enable the assembly of tetrazoles, which also opens a new entry to amides based tetrazole synthesis based on metal-free protocol. Other fascinating merits of this new protocol are operational simplicity; excellent yields of products in short reaction times and easy workup procedures.

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